## REMARKS

On February 10, 2010 applicants filed an amendment in this case in response to the final rejection of December 10, 2009. In the Advisory Action of February 26, 2010 the Examiner indicated that the February 10, 2010 amendment would not be entered for purposes of appeal. Accordingly, applicants submit this supplemental amendment in response to the final rejection. The claim markings indicate the amendments relative to the claims as filed August 5, 2009, which was the last amendment entered.

In a telephone conference on March 17, 2010, the Examiner indicated that the claim amendments made above would be entered for purposes of appeal. The courtesy and cooperation of the Examiner are acknowledged with appreciation.

The present invention relates to an immunostimulant composition comprising the combination of an agonist for a Toll-like 7 receptor (TLR 7) and an agonist for a Toll-like 4 receptor (TLR 4). The applicants have found, surprisingly, that the combination of these two agonists in a single composition provides significantly more potentiated results (stronger Th1 orientation as measured by IL-12 production by human cells) compared to what would have been expected based on the results achieved with each agonist used independently of the other. This potentiated response is surprising because previous experiments had shown that when two or more immunostimulants are present in the same composition it is "difficult to increase the response already obtained with a single immunostimulant." ('009 publication at [0036]) In the examples of the specification, the agonist of the TLR 4 receptor is ER804057, and the agonist of the TLR 7 receptor is 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol (also known as R-848).

Claim 1 is amended herein to limit the TLR 7 receptor to 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol for which there is data in the specification. Claims 4 and 5 are accordingly canceled herein.

This amendment does not require additional search or consideration.

The rejection of the pending claims as obvious over Hawkins et al. (U.S. 6,290,973), Gerster et al. (U.S. 5,389,640), and the Jannsens et al. article is respectfully traversed.

Hawkins is cited for its disclosure of immunological adjuvant compounds, one of which is ER804057. Dozens of other compounds are also disclosed. Data is presented for many of these compounds, and schemes for synthesis are presented for many others. No data or synthetic scheme is presented for ER804057. There is no suggestion that any such compound should be combined with another compound to produce a potentiated immunostimulant effect.

Gerster is cited for its teaching of imidazole-quinoline compounds as antivirals. Gerster also teaches that some of those compounds induce biosynthesis of interferon-α.

Jannsens et al. is cited for its teaching at page 639 that "TLR7 and TLR8 have been shown to recognize antiviral compounds with strong immunostimulatory capacity belonging to the group of imidaquinolines." Jannsens also teaches that one group of pathogens is not exclusively recognized by one TLR, and one TLR can respond to many structurally unrelated ligands, which are often derived from different groups of pathogens. Other TLRs are ligand-specific and appear to recognize only one type of ligand. (p. 638, second column, bottom paragraph).

None of these references, taken alone or in combination, teaches or suggests (1) the ratio of IgG1/IgG2a could be lowered by appropriate choice of a combination of TLR agonsits, (2) that different TLR agonists be combined in a single immunostimulant composition, (3) that a combination of different TLR agonists would result in enhanced potentiation of the Th1 type response, (4) that a combination of TLR 4 agonists and TLR7 agonists would provide an immunostimulant composition that potentiates a Th1-type response greater than the response achieved with either agonist alone, or (5) that a combination of 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol with a TLR 4 agonist would provide an unexpectedly superior immunostimulant response. The Examiner is respectfully referred to the table at page 4 of the published application, between paragraphs [0067] and [0068]. It is seen that the IgG1/IgG2a ratio at day 32 for the combined TLR4 agonist and 4-amino-2-ethoxymethyl-α,α-dimethyl-1-

H-imidazo[4,5c]quinoline-1-ethanol is 0.9, compared to 3.5 for the TLR4 agonist alone and 1.3 for the TLR7 agonist alone. This data demonstrate that the result achieved with the combination of the TLR4 agonist and 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol is greater than what would have been expected from either agonist taken alone.

For purposes of comparison, the previously submitted Declaration of Nicolas Burdin, PhD. reported data on compositions in which the TLR 4 agonist was combined with a TLR2 agonist. The data indicated that the combination of the two receptor agonists did *not* lead to improved results, and for some tests the results were actually *worse* than the results achieved when only one of the receptors was used. (Decln. ¶6). This comparative data was submitted to show that not all combinations of TLR4 agonists with other TLR agonists are effective. This data is consistent with the statement in the specification (publication paragraph [0036]) that "when 2 or more immunostimulants are present in the same composition, it is difficult to further increase the response already obtained." In particular, it would not have been obvious to one skilled in the art that the combination of a TLR4 agonist with a TLR7 agonist would produce an enhanced Th1 type potentiated response. And it would not have been obvious that 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol when combined with a TLR 4 agonist would led to improved results

The case *In re Kerkhoven* is cited in the Action for the proposition that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." But the presently claimed combination possesses an unexpected property, i.e., it *potentiates* a Th1-type response (as emphasized by the amendment to claim 1 made herein). That is, the combination of the TLR4 agonist and 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol is synergistic, a result not suggested by or predictable from the prior art. And the non-obviousness is further enhanced by the fact that not all combinations of TLR agonists are synergistic. The prior art does not suggest combining TLR agonists, let alone that certain combinations would by synergistic while others not, nor, in particular, that the

combination of TLR4 agonist and 4-amino-2-ethoxymethyl-α,α-dimethyl-1-H-imidazo[4,5c]quinoline-1-ethanol, among all possible combinations, would be synergistic while other combinations are not. Consequently, the claims as presently amended are not obvious over the cited art.

## CONCLUSION

In view of the foregoing, a Notice of Allowance is respectfully requested. The applicants invite the Examiner to contact the Applicants' undersigned representative if the Examiner believes that this would expedite prosecution of this application

Respectfully submitted,

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